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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,641	KROETZ ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-41* is/are pending in the application.

4a) Of the above claim(s) *19-20 and 35-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18,21-23,26-34 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. By Amendment filed June 13, 2006, claims 14 and 30 have been amended and claims 42-45 have been newly added.

2. Acknowledgment is made of applicant's filing of Declaration on June 13, 2006.

3. Acknowledgment is made of applicant's affirmation of the invention of Group I Invention along with the subgenus compounds (Z=O, W=C, X and Y= N, R2 and R4=H) as the elected species. Claims 19-20 and 35-36 were withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Claims 14-18, 21-23, 26-34 and 37-45 are currently pending for prosecution on the merits.

Summary of Action

5. The rejection of claims 14, 21-23, 26-30 and 37-41 under 35 USC, first paragraph, for the lack of written description is not maintained in light of the amendment/remarks filed June 13, 2006.

6. The rejection of claims 15-18 and 31-34 under 35 USC 112, first paragraph, for the lack of scope of enablement is not maintained for the reasons of record in light of the amendment/remarks filed June 13, 2006. However, the rejection of claims 14, 21-23, 26-30 and 37-41 under 35 USC 112, first paragraph, for the lack of scope of enablement is maintained for the reasons of record

7. The rejection of claims 14-18, 21-22, 30-34 and 37-38 under 35 U.S.C. 102(b) as being anticipated by Ichihara et al. (JP 07304755) is maintained for the reasons of record.

8. The rejection of claims 14-18, 21-23, 27-34 and 37-40 under 35 U.S.C. 102(e) as being anticipated by Blum et al. (US 5962455) is maintained for the reasons of record.

9. The rejection of claims 26 and 41 under 35 U.S.C. 103(a) as being unpatentable over Blum et al. (US 5962455), and further in view of The Merck Manual ("Hypertension", Fifteenth Edition, 1987) is maintained for the reasons of record.

10. The rejection of claims 30-34 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5 of prior U.S. Patent No. 6,531,506 is not maintained in light of the amendment/remarks filed June 13, 2006.

11. The rejection of claims 14-18, 21-23, 26-34 and 37-41 under the judicially created doctrine of double patenting over claims 6-9 of U. S. Patent No. 6,531,506 is maintained for the reasons of record.

12. Applicant's amendment requiring the limitation of "("sHE"), which inhibitor inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM" (claims 14 and 30), "totally inhibits the epoxide hydrolyzing activity of sHE at a concentration of 100 μM" (new claims 42 and 43) and "the inhibitor is administered in a total daily dose from about 0.001 μM/kg to about 100mg/kg body weight of the patient" (new claims 44-45) necessitates a new ground of the rejection in this Office Action.

Claim Objections

13. Claims 14 and 30 are objected to because of the following informalities: Abbreviation of soluble epoxide hydrolase should be enclosed within parenthesis without quotation mark so as to avoid confusion. Appropriate correction is recommended.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 42-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims in this application introduce new limitation into the claimed invention, namely "said inhibitor totally inhibits the epoxide hydrolyzing activity of sEH at a concentration of 100 μM". The examiner determines that when all evidences in the original disclosure are considered and carefully reviewed, the newly amended claims fail to find support in the original specification.

Applicant states in the argument/remarks filed June 13, 2006 (page 8) that new claims 42 and 43 are supported, inter alia, by the disclosure of US Application No. 09/252,148, now USP 6,150,415, at e.g., column 7, lines 20-33, showing that compound 2 (DCU) inhibited sEH activity by 99.3%± 0.8 at 100 μM.

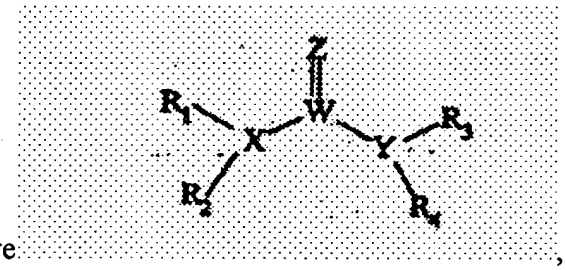
The American Heritage Dictionary (Second College Edition, 1982) defines the term "total" as "the amount or quantity obtained by addition; a whole quantity or entirely"; "inhibit" as "prevent"; and "prevent" as "to keep from happening". The interpretation of the instant claims

"totally inhibits the epoxide hydrolyzing activity of sEH at a concentration of 100 μM " allows for the inclusion of complete inhibition or prevention (100%) at all times.

Unlike the concept of the complete prevention of sEH activity at all times, the specification only shows variable inhibitions (ranges from 98.5 to 101% at 100 μM).

As stated above, about 99.3% inhibition is not considered equal to 100% inhibition or prevention. The skilled artisan would have not interpreted as "total inhibition" as to the claims 42 and 43. There is no express statement about "total inhibition" or "complete prevention" can be found in the specification. Thus, "total inhibition" of epoxide hydrolyzing activity of sEH by said inhibitor, in fact, introduces new matter. The new limitation recited in the present claims, which did not appear in the specification filed, introduces new concepts and violate the description requirement of the first paragraph of 35 USC 112.

15. Claims 14, 21-23, 26-30 and 37-45 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the treatment of hypertension with the soluble epoxide hydrolase inhibitor represented by the



structure, does not reasonably provide enablement for "inhibitor of soluble epoxide hydrolase" or "an inhibitor of soluble epoxide hydrolase inhibtor (sHE) which inhibitor inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM". The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: the nature of the invention; the state of the prior art; the relative skill of those in the art; the predictability or unpredictability of the art; the breadth of the claims; the amount of direction or guidance presented; the presence or absence of working examples; and the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The present invention are drawn to a method of reducing blood pressure or hypertension in a patient comprising administering an inhibitor of soluble epoxide hydrolase having characteristic of "inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM".

The interpretation of the instant claims allows for the inclusion of any known sHE inhibitor having "50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM" that are known to exist and those that may be discovered in the future.

The specification discloses compounds of the Formula 1, which can be prepared by methods disclosed in USSN 09/252,148, as the preferred class of compounds that exhibits the activity of inhibiting soluble epoxide hydrolase (see para. [0007] and [0034]). The specification discloses that the preferred compounds of the invention have an IC50 of less than about 500μM, and provides various exemplary compounds that were tested for their inhibition of MsEH and

HsEH (see para. [0008] and Table 1) by the in vitro assays (para. [0041]-[0042]). In addition to the compounds of the formula 1, the compounds of the formula 2, which can be prepared and assayed by methods disclosed in US 5,955,496 and WO 98/06261), are disclosed as the second preferred class of compounds ([0009], Table 2 and [0034]).

Furthermore, the specification provides the study in rat and provides that the inhibition of sHE, particularly when N-cyclohexyl-N'-dodecylurea, N-cyclohexyol-N'-ethylurea and dodecylamine which read on the Formula I structure is administered to rat, is capable of decreasing blood pressure in rat (Example).

It is generally recognized in the art that biological compounds often react unpredictably under different circumstances (Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)). Similarly, the pharmacological property of sHE inhibitors (even if they have equal potency) are known to behave differently under different circumstances (see Morisseau et al., American Society of Pharmacology and Experimental Therapeutics, abstract, Vol. 316, No. 2:815-821, particularly "Interpretive Summary"). Morisseua states: "The pharmacological properties of soluble epoxide hydrolase (sEH) inhibitors are being investigated for the treatment of hypertension, atherosclerosis, and inflammatory diseases. However, the pharmacological targets of these potential drugs have not been fully explored. This study found that one such sEH inhibitor, 1-cyclohexyl-3-dodecyl urea (CDU), inhibited the growth of multiple vascular cell types independent of an effect on the sEH, while other equally potent inhibitors and the endogenous epoxy fatty acid substrates of the target enzyme did not possess these properties. This study suggests that greasy cyclohexyl-ureas may have useful

anti-proliferative properties, and caution against interpretation of biological effects when only found using micromolar concentrations of poorly characterized pharmacological agents".

The relative skill of the artisan and the unpredictability of the pharmaceutical art is very high. To practice the instant invention to the claimed scope, applicant have to (i) make or synthesize numerous possible compounds characterized as "an inhibitor of soluble epoxide hydrolase" in view of the structure-activity relationship of the compounds, (ii) screen potentially suitable compounds and (iii) assay to find out which compounds are able to "inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM", and then (iv) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the result provided in the instant specification to the larger and highly varied genera of compounds that are characterized by "an inhibitor of soluble epoxide hydrolase inhibtor (sHE) which inhibitor inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM", without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or

different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of exemplified "sEH" wherein the desired therapeutic activity are linked to the pharmacophores of structure Formula 1 or Formula 2, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed "an inhibitor of soluble epoxide hydrolase inhibtor (sHE) which inhibitor inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM" that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such

that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

16. Claims 14-18, 21-22, 30-34 and 37-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Ichihara et al. (JP 07304755).

Ichihara teaches use of compounds (e.g., RN 174398-90-4, RN 174398-91-5, RN 174398-92-6, RN 174398-93-7, etc...) or their salt, which reads on the instantly claimed compounds of the formula 1, for the treatment of the claimed cardiovascular disease such as hypertension by modulating rennin-angiotenisn system, wherein said compound is administered in various dosage forms including oral dosage forms (i.e., tablet, capsule), see para. [0001], [0035] and Table I). Ichihara discloses that a rennin inhibitor tends to control generation of angiotensin II which works powerfully to pressure ups, such as a vasoconstrictor action and aldosterone secretion, by checking the reaction of the rennin and rennin substrate (angiotensiongen) which are called rate-determining step of the rening-angiogensin series which is a pressure-up system in the living body, and reducing generation of angiotensin I (para. [0002]).

Although Ichihara is silent about the functional characteristic of said compounds in inhibiting soluble epoxide hydrolase, such property or characteristic deems to be inherent to the compounds disclosed by Ichihara which read on the claimed structure compounds. Thus, Ichihara anticipates the claimed invention.

17. Claims 14-18, 21-23, 27-34 and 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Blum et al. (US 5962455).

Blum teaches use of compounds (e.g., RN 202472-67-1, RN 202472-68-2, RN 202472-69-3, RN 202472-70-6,etc...) or their salt, which reads on the instantly claimed compounds of the formula 1, for the treatment of the claimed cardiovascular disease such as hypertension or essential hypertension as well as congestive heart failure, wherein said compound is administered in dosage amounts of from about 0.1mg to about 140mg per kilograms of body weight per day and in various dosage forms including oral dosage form (abstract; column 1, line 39; column 1, line 45 thru column 3, line 15; column 7, line 51; column 8, line 52 thru column 10, line 62).

Although Blum is silent about the functional characteristic of said compounds in inhibiting soluble epoxide hydrolase, such property or characteristic deems to be inherent to the compounds disclosed by Blum which read on the claimed structure compounds. Thus, Blum anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 26 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blum et al. (US 5962455), and further in view of The Merck Manual ("Hypertension", Fifteenth Edition, 1987).

The teaching Blum has been discussed in above 35 USC 102(e) rejection.

The Merck Manual is being supplied a supplemental reference to demonstrate the routine knowledge in using antihypertensive in treating hypertension, essential hypertension and/or systolic hypertension.

The teaching of Blum differs from the claimed invention in the use of said compounds in reducing systolic blood pressure.

However, one having ordinary skill in the art would have expected at the time of the invention was made that the known antihypertensive agent as taught by Blum would also be effective in reducing systolic blood pressure. Since the prior art does not distinguish the utility of known anti-hypertensive medications for only systolic blood pressure management, the skilled artisan would have expected that the Blum's compounds having antihypertensive effect would provide benefit for the patient having systolic blood pressure and/or diastolic blood pressure.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 14-18, 21-23, 26-34 and 37-41 are rejected under the judicially created doctrine of double patenting over claims 2-9 of U. S. Patent No. 6,531,506 as applied to claims 14-18, 21-23, 27-34, 37-39 and 42-45 26, and further in view of The Merck Manual ("Hypertension", Fifteenth Edition, 1987).

With respect to the obviousness of the claims 14-18, 21-23, 26-34 and 37-45 over claims 2-9 over US'506,

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed characteristic or property of having "50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM" or "totally inhibits the epoxide hydrolyzing activity of sEH at a concentration of 100 μM" must be inherently presented in the referenced compounds. Since the patent directing the administration of compound(s) or compounds represented by the identical structure having epxoide hydrolase inhibiting activity (e.g., dicyclohexyurea) inherently possessing a therapeutic effect for the same ultimate purpose (for the treatment of hypertension) as disclosed by applicant anticipates applicant's claim. Thus, the patent makes obvious the instant invention.

Regarding the instantly claimed "the patient is at risk for cardiovascular disease, renal, or stroke" (claims 28-29), since the referenced hypertension "metes and bounds" the instant limitation, the patent makes obvious the instant invention.

With respect to the obviousness of the claims 26 and 40-41,

As discussed above, However, one having ordinary skill in the art would have expected at the time of the invention was made that the agent that are known to be effective as antihypertensive agent would also be effective in reducing systolic blood pressure. Since the prior art does not distinguish the utility of known anti-hypertensive medications for only systolic blood pressure management, the skilled artisan would have expected that the Blum's compounds having antihypertensive effect would provide benefit for the patient having systolic blood pressure and/or diastolic blood pressure.

Response to Arguments

Applicant's arguments with respect to claims 14-18, 21-23, 26-34 and 37-45 have been considered but are moot in view of the new ground(s) of rejection.

20. Applicant's argument(s) with respect to the rejection of claims 14, 21-23, 26-30 and 37-41 35 USC 112, 1st paragraph, for the lack of written description have been fully considered and are persuasive. Accordingly, this rejection has been withdrawn.

21. Applicant's argument(s) with respect to the rejection of claims 14-18, 21-23, 26-34 and 37-41 under 35 USC 112, 1st paragraph, for the lack of enablement have been fully considered and are persuasive only respect to the scope of the enablement for the claims 15-18 and 31-34. Accordingly, the rejection of claims 15-18 and 31-31 has been withdrawn.

22. Applicant's argument(s) with respect to the rejection of claims 14, 21-23, 26-30 and 37-41 under 35 USC 112, 1st paragraph, for the lack of enablement have been fully considered but are moot in view of the new of rejection(s) as discussed above.

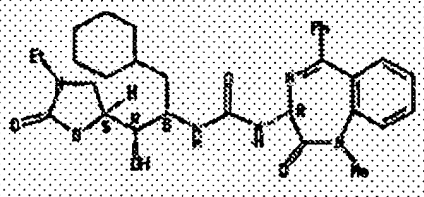
23. Applicant's argument(s) and Declaration filed June 13, 2006 with respect to the rejection of claims 14-18, 21-22, 30-34 and 37-38 under 35 U.S.C. 102(b) have been fully considered but they are not persuasive.

Applicants respectfully call the Examiner's attention to the accompanying Declaration of Dr. Bruce D. Hammock. Dr. Hammock, a co-inventor of the current application, holds the position of Distinguished Professor at the University of California at Davis and was elected to membership in the National Academy of Sciences in 1999. As attested to in the Declaration, he is also an author or co-author of over 600 articles in the scientific literature, of which well over 200 relate to the study of epoxide hydrolases, their activity, and the effects on inhibiting them. He further states that many of his recent publications have focused in particular

on studying the activity of the enzyme soluble epoxide hydrolase ("sEH") and the effects of inhibiting the ability of sEH to hydrolyse epoxides.

While the Examiner is respectfully requested to carefully review the entirety of the Declaration, the Examiner's attention is specifically directed to the following. Dr. Hammock states that his laboratory has now studied the structure activity relationship ("SAR") of over 2000 compounds (Declaration, at ¶ 6), and has crystal structures of both the murine and the human sEH enzyme bound to selected inhibitors. *Id.* He further declares that, as a result of these studies, he can now predict with a high degree of confidence what urea-based compounds will inhibit human sEH and which will not. *Id.*

Dr. Hammock was provided with the structures of each of the compounds from the Ichihara reference cited by the Action as taught by the reference for the treatment of cardiovascular disease. Based on the extensive SAR studies mentioned above, Dr. Hammock is able to state that the compounds cited would be inactive to poor inhibitors of sEH at physiologically relevant concentrations. (He notes that he puts in this qualification since many otherwise inactive compounds are capable of inhibiting an enzyme's activity if present at concentrations beyond those that can be achieved *in vivo*.) With regard to the first compound cited, RN 174398-90-4,

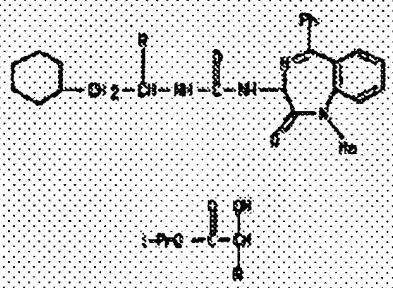


Dr. Hammock states:

> On the left side of the urea, the R group is too big and there is a polar group too close to the NH of the urea. The group to the right of the urea also has polar residues too close to the urea. Even with a highly potent group on the right side of the urea, the group on the left side would preclude activity. The crystal structure of the sEH enzyme shows a very hydrophobic catalytic tunnel except

for very specific locations. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

Declaration at ¶ 10, Part A. Similarly, with respect to the second compound cited, RN 174398-91-5,



Dr. Hammock states:

The group to the right side of the urea is too bulky and the R groups on both sides of the urea have polar groups too close to the urea. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

Declaration, at ¶ 10, Part B. Dr. Hammock also predicts that the other two compounds disclosed by Ichihara and cited by the Action as anticipating the invention likewise contain groups that are too bulky or polar to permit them to inhibit the enzyme. See, Declaration, at ¶ 10, Parts C and D.

Dr. Hammock also comments on the compounds not expressly cited but that are set forth in a 2 page table at the end of the Ichihara reference. Dr. Hammock notes that, according to the structure on page 735, almost all have a 7-membered, heterocyclic ring with a substituted carbon next to the L1 substituent. Declaration, at ¶11. He states that these compounds will be inactive as sEH inhibitors because the 7-membered unsaturated ring will not fit into the active site of the enzyme. Declaration, at ¶11. He also notes that one compound on the table does not fall within Formula I. *Id.*

The rejection is based on an incorrect premise. Neither the compounds identified by the Action nor the other compounds disclosed in Ichihara but not specifically commented on by the Action would be active as sEH inhibitors at physiologically relevant concentrations. Accordingly, the rejection should be reconsidered and, Applicants submit, withdrawn.

This argument is not found persuasive. Declaration containing opinion evidence of criticality of the activity of the sHE inhibitor having 50% the epoxide hydrolyzing activity of

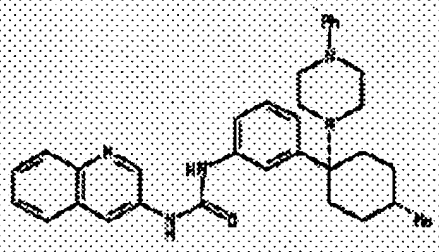
sHE at a concentration of less than about 500 μM is inadequate to overcome the rejection based on the prior art (Ichihara) because there is no factual evidence supporting the statement.

Unlike the applicant's argument, the referenced species of Ichihara (which reads on the generic structure of the instant claim 15 or 31) are known to have antihypertensive activity regardless of the alleged "inhibitor inhibits by 50% the epoxide hydrolyzing activity of she at a concentration of less than about 500 μM).

Due to the absence of tests (the activity of anti-hypertensive activity) comparing the applicant's sHE inhibitor which inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM with the Ichihara, the examiner maintains that the applicant's argument of unexpected or superior results constitute mere argument.

23. Applicant's argument(s) and Declaration filed June 13, 2006 with respect to the rejection of claims 14-18, 21-23, 27-34 and 37-40 under 35 U.S.C. 102(e) as being anticipated by Blum et al. (US 5962455) have been fully considered but they are not persuasive.

Dr. Hammock was provided with the structures of each of the compounds from the Blum reference cited by the Action as taught by the reference. Based on the extensive SAR studies of some 2000 compounds mentioned above, Dr. Hammock predicts that the compounds cited would be inactive as inhibitors of sEH at physiologically relevant concentrations. See, Declaration, at §12. With regard to the first compound cited, RN 202472-67-1,

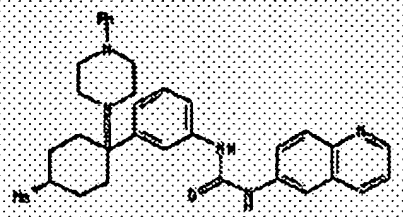


• 3 HCl

Dr. Hammock states:

> There is a slight chance the group on the left of the urea would yield activity with the correct substituents on the other side. However, the activity should be mediocre to poor. The group on the right is too large. I predict as well that the heterocycle will be far too polar. Accordingly, I predict that this compound would have poor to no activity as an inhibitor of sEH.

Declaration, at ¶ 12, Part A. Similarly, for the second compound, RN 204272-68-2,



• 3 HCl

Dr. Hammock states:

> This compound is similar to the one discussed [the compound of RN 204272-67-1] above, except that the sides are reversed. For the same reasons as set forth with respect to the preceding compound, I predict that this compound would have poor to no activity as an inhibitor of sEH.

Declaration, at ¶ 12, Part B. Dr. Hammock also predicts that the other two compounds disclosed by Blum and cited by the Action as anticipating the invention likewise contain groups that are too bulky or polar to permit them to inhibit the enzyme. See, Declaration, at ¶ 12, Parts C and D.

With respect to the other compounds disclosed in Blum but not specifically identified by the Action, Dr. Hammock notes that a polar group closer to the urea carbonyl than about 6 angstroms will eliminate the compounds from having activity as an inhibitor of sEH, and that this precludes many of the Blum compounds from having activity as inhibitors of sEH. Declaration, at ¶13. He further notes that many of the compounds listed in the general structures have R and R' groups on the 1 and 3 positions of the urea that will not confer activity. *Id.* Additionally, he notes that the majority of the general structures disclosed in Blum have very large and branched chain groups close to the urea which would dramatically reduce affinity for the enzyme. *Id.* He states that none of them have structures that would lead him to expect that they would inhibit sEH at physiologically relevant concentrations. *Id.* Finally, he notes that these compounds were designed to bind to the neuropeptide Y1 receptor, which of course has its own very specific properties, and that one would be very surprised if a similar structure activity relationship was observed between a peptide receptor and an enzyme dealing with highly lipophilic fatty acid oxides. *Id.*

The rejection is based on an incorrect premise. Neither the compounds identified by the Action as disclosed by Blum and expressly or inherently reading on the claims as presented nor the other compounds disclosed in Blum but not specifically commented on by the Action would be active as sEH inhibitors in physiologically relevant concentrations. The person of skill would recognize that such poor inhibitors would have to be administered in such large amounts that they would not be therapeutically useful agents. Accordingly, the rejection should be reconsidered and, Applicants submit, withdrawn.

This argument is not found persuasive. Declaration containing opinion evidence of criticality of the activity of the sHE inhibitor having 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM is inadequate to overcome the rejection based on the prior art (Ichihara) because there is no factual evidence supporting the statement.

Unlike the applicant's argument, the referenced species of Blum (which reads on the generic structure of the instant claim 15 or 31) are known to be useful as antihypertensive agent regardless of the alleged "inhibitor inhibits by 50% the epoxide hydrolyzing activity of she at a concentration of less than about 500 μM).

Due to the absence of tests (the activity of anti-hypertensive activity) comparing the applicant's sHE inhibitor which inhibits by 50% the epoxide hydrolyzing activity of sHE at a concentration of less than about 500 μM with the Ichihara, the examiner maintains that the applicant's argument of unexpected or superior results constitute mere argument.

24. Applicant's argument(s) and Declaration filed June 13, 2006 with respect to the rejection of claims 26 and 41 under 35 U.S.C. 103(a) as being unpatentable over Blum et al. (US 5962455), and further in view of The Merck Manual ("Hypertension", Fifteenth Edition, 1987) have been fully considered but they are not persuasive.

As noted in the preceding section, none of the compounds disclosed by Blum, whether expressly cited by the Action or otherwise described in the reference, are predicted to inhibit the epoxide hydrolase activity of sEH at physiologically active concentrations. Accordingly, Blum does not teach, alone or in combination with the Merck Manual, compounds which read on claims 26 and 41. Reconsideration and withdrawal of the rejection are respectfully requested.

This argument seems to be basically the same rejection as discussed above, so the response discussed above applies here as well. Thus, the examiner maintains that the references in combination (Blum and the Merck Manual) makes obvious the instant invention.

25. Applicant's arguments with respect to the rejection of claims 30-34 under 101 as claiming the same invention as that of claims 1-5 of prior U.S. Patent No. 6,531,506 have been fully considered and persuasive. Accordingly, this rejection has been withdrawn.

26. Applicant's arguments with respect to 14-18, 21-23, 26-34 and 37-41 under the judicially created doctrine of double patenting over claims 6-9 of U. S. Patent No. 6,531,506 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the recitation of "the inhibitor of sHE inhibits activity of the enzyme by 50% at a concentration of less than about 500 micromolar" makes the instant claims patentably distinctive further over claims 6-9 of the USP'506.

The examiner strongly disagrees with this argument. Both compounds represented by the instant formula (in claim 15 and 31) and the referenced formula (in claim 2) are directed to the same compounds. Thus, the USP'506 directing the administration of the same compounds to the same patient population in overlapping dosage amounts as the instant claims (a total daily dose from about 0.001 μM/kg to about 100 mg/kg body weight of the patient, compare the instant claim 23 over the referenced claim 8) inherently possessing the same therapeutic effect as the same ultimate purpose as disclosed by applicant anticipates the claimed invention even absent

explicit recitation of underlying mechanism such as "inhibitor of sHE inhibits activity of the enzyme by 50% at a concentration of less than about 500 micromolar". Thus, the reference makes obvious the instant invention.

Conclusion

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Patent Examiner
AU 1614